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PATENT
Attorney Docket No. 03495.0059-06000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
BLAUDIN DE THE et al.	
Serial No.: 07/649,342	Group Art Unit: 1812
Filed: February 1, 1991	Examiner: J. Ulm
For: A NOVEL STEROID/THYROID HORMONE RECEPTOR-RELATED GENE INAPPROPRIATELY EXPRESSED IN HUMAN HEPATOCELLULAR CARCINOMA	

94-1465

APPELLANTS' BRIEF ON APPEAL

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Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

APPELLANTS' BRIEF ON APPEAL

This is an Appeal from the Examiner's final rejection of Appellants' claims.

I. STATUS OF CLAIMS

Claims 1-14, 24-34, 39-57 and 59 are the claims on appeal. All other claims have been cancelled except for claim 58, which has been withdrawn from consideration. No claim stands allowed.

II. STATUS OF AMENDMENTS

Claims 1-14, 24-34, 39-57 and 59 were finally rejected in an Office Action dated July 8, 1992 (Paper No. 21). A response to the final rejection was filed January 7, 1993. In an Advisory

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Action dated March 9, 1993 (Paper No. 23), the Examiner indicated that Appellants' response was not deemed to place the application in condition for allowance.

A Supplemental Amendment was filed on April 15, 1993, in which the dependency of claims 46 and 55 was amended. The Examiner indicated in an Advisory Action dated May 4, 1993 (Paper No. 25), that these amendments would be entered upon filing an appeal.

A copy of the appealed claims can be found in the Appendix. The claims have been grouped based on order of dependency.

III. SUMMARY OF THE INVENTION

Retinoic acid is a member of a class of compounds generally referred to as retinoids. These compounds exhibit effects on cell proliferation, differentiation and pattern formation during development. Retinoic acid produces its effect on the cell by binding to receptors in the cell nucleus.

Appellants have identified a DNA sequence encoding a new member of the nuclear hormone receptor family that responds to retinoic acid. In particular, Appellants' claims define the cloned DNA sequence of the new retinoic acid receptor RAR-β, which is identified in the subject application as the *hap* (for "hepatoma") gene.

Both the nucleotide sequence of the cloned DNA sequence and the amino acid sequence of the receptor encoded by the cloned DNA sequence have been elucidated by Appellants. (See page 6, lines 1-22 and the paragraph bridging pages 7 and 8.) The RAR-β

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receptor is related to the steroid/thyroid hormone receptors. (See, for example, page 12, lines 10-12.)

IV. ISSUE

The issue on appeal is whether claims 1-14, 24-34, 39-57 and 59 are unpatentable under 35 U.S.C. §103 over Petkovich et al. (Nature 330:444-450, 1987) in view of Hauptmann et al. (Nucleic Acids Research 13:4739-4749, 1985) and Krust et al. (EMBO J. 5:891-897, 1986), even though none of the references teaches or suggests a DNA sequence encoding a retinoic acid receptor structurally similar to Appellants' RAR-β.

The Petkovich et al. article was cited by the Examiner as teaching a cloned DNA sequence encoding the retinoic acid receptor RAR-α, which has regions of varying degrees of homology to Appellants' retinoic acid receptor RAR-β. (See Paper No. 12, page 3.)[1/]

The Hauptmann et al. article was cited as teaching the use of a cloned DNA sequence to identify other DNA sequences encoding functionally related proteins. Retinoic acid receptors are not mentioned.

The Krust et al. article was relied upon by the Examiner as teaching functionally conserved and non-conserved regions of

---

1/ The Examiner also stated that "Applicants contribution consists of isolating a DNA corresponding to a gene whose existence was disclosed prior to the instant invention by Petrovich et al. [sic, Petkovich et al.]. . . ." Paper No. 23 at 2. The statement implies that the claims are anticipated, but a rejection was not made under §102. In fact, the DNA claimed is not the same as Petkovich's DNA.

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steroid-related receptor proteins. (See Paper No. 12, pages 3-4.) Again, retinoic acid receptors are not mentioned.

Appellants' DNA sequence and the gene disclosed in Petkovich et al. are two different members of the retinoic acid receptor family and are so recognized in the art. Brand et al., Nature 332:850 (1988). Three distinct and different members of this receptor family have been identified. The original member of the family, named RAR-α, was identified by Giguere et al., Nature 330:624-629 (1987) as well as by Petkovich et al. Appellants' cloned DNA sequence encodes the second member of this family, RAR-β. (Brand et al. acknowledged that "the existence of the human-retinoic acid receptors designated RAR-α and RAR-β" has been demonstrated.) The third member, RAR-γ, was identified by Zelent et al., Nature 339:714-717 (1989). The cited references have been made of record in the subject application.

V. GROUPING OF CLAIMS

Appellants' claims can be divided into three independently patentable groups:

Group I comprising claims 1-3, 10-14, 24-34, 40, 43-45 and 53;

Group II comprising claims 4-9 and 57; and

Group III comprising claims 39, 41, 42, 46-52, 54-56 and 59.

The claims in these groups do not stand or fall together.

The cloned DNA sequence encoding the retinoic acid receptor RAR-β and its use are covered by the claims of Group I.

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Claims 4-9 and 57, the claims of Group II, define a DNA fragment comprising a nucleotide sequence selected from six sequences of RAR-β.

The claims of Group III are directed to a 72 base pair nucleotide sequence, which extends the cloned DNA sequence of Group I, and its use.

VI. ARGUMENT

It is Appellants' position that the Examiner has not made a case of *prima facie* obviousness because of the vast differences in structure between the claimed DNA encoding Appellants' RAR-β and the DNA described in the prior art. Accordingly, Appellants traverse the rejection of claims 1-14, 24-34, 39-57 and 59 under 35 U.S.C. §103 over Petkovich et al. in view of Hauptmann et al. and Krust et al.

A. APPELLANTS' INVENTION WOULD NOT HAVE BEEN *PRIMA FACIE* OBVIOUS IN VIEW OF PRIOR ART THAT DOES NOT SUGGEST THE NUMEROUS STRUCTURAL MODIFICATIONS NEEDED TO OBTAIN APPELLANTS' DNA

The Court of Appeals for the Federal Circuit and its predecessor court, the Court of Customs and Patent Appeals, have indicated that a case of *prima facie* obviousness for a chemical compound can be based on structural similarity if the close similarity gives rise to an expectation that compounds similar in structure will have similar properties. See In re Merck & Co., 800 F.2d 1091, 1096-1098, 231 U.S.P.Q. 375, 379-380 (Fed Cir. 1986), citing In re Payne, 606 F.2d 303, 313, 203 U.S.P.Q. 245,

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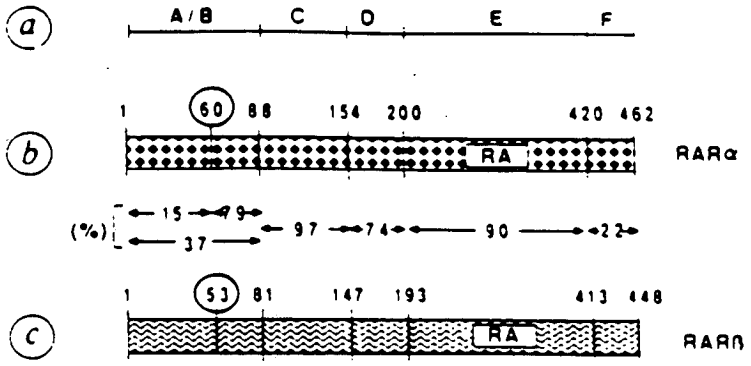
254 (CCPA 1979). The rule is, of course, based on the premise of structural similarity between the claimed compound and the prior art compound. Structural similarity sufficient to establish *prima facie* obviousness is non-existent in this case.

The nucleotide sequence of the RAR-β gene of the present invention is disclosed on page 6, lines 1-22, of the present application. Comparison of the sequence of the RAR-β gene with that of the RAR-α gene disclosed in Figure 2 of Petkovich et al. highlights the differences between the two sequences. The nucleotide sequence of Appellants' cloned DNA is different from the RAR-α gene of Petkovich et al.

That the degree of homology between the Appellants' DNA sequence and the sequence of Petkovich et al. varies throughout the molecule is shown by the following figure, which is a schematic representation of the homology between RAR-α and RAR-β.



The figure is from Brand et al., Nature, 332:850-853 (1988), which is of record.

Lines (b) and (c) of the figure represent the RAR-α protein and the RAR-β protein, respectively. The receptors RAR-α and

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RAR-β are typically divided into six regions, A-F, as shown diagrammatically in line (a) of the above figure. The degree of homology between the two receptors is indicated in the space between lines (b) and (c). The degree of homology represents the extent of amino acid identity between the two receptors throughout various regions encoded by the DNA.

It is clear from a comparison of the sequences that the homology between the receptor of Petkovich et al., RAR-α, and Appellants' receptor, RAR-β, is as low as 15% and 22% in the end regions. The two genes are only distantly related with significant differences in amino acid sequence.

The Federal Circuit has made it clear that generalizations should be avoided insofar as specific chemical structures are alleged to be *prima facie* obviousness one from the other. In re Grabiak, 769 F.2d 729, 731, 226 U.S.P.Q. 870, 871-872 (Fed. Cir. 1985). Moreover, where the claimed chemical compound has only remote homology to the prior art compound, there is no presumption of obviousness of the claimed invention. See In re Mills, 281 F.2d 218, 126 U.S.P.Q. 513 (CCPA 1960) ("Where, as here, the invention for which a patent is sought relates to one member of an homologous series and the disclosure of the prior art is of a non-adjacent member of the series, In re Henze . . . is not authority for a 'legal presumption' of obviousness of the claimed invention.")

It is evident that it must be the Examiner's view that the numerous differences in the nucleotide sequences of Appellants' RAR-β gene and Petkovich's RAR-α gene do not affect the

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equivalency of these genes. In other words, one can substitute one nucleotide for another, one by one in Petkovich's gene, without conserving the amino acid sequence encoded by the gene, and expect that the substitutions will to have no material effect on the resulting DNA molecule. As the Court stated in In re Mills, supra:

> If the Patent Office wishes to rest a rejection on chemical theory, it is its duty to support its case with adequate evidence of the existence and meaning of that theory.

281 F.2d at 223-4, 126 U.S.P.Q. at 517. Absent from this record is any evidence to support the nucleotide substitution theory on which the rejection must be based. The failure of the secondary references (Hauptmann et al. and Krust et al.) to support such a theory cannot be seriously disputed.

The Examiner stated during prosecution that "[t]he Petrovich [sic, Petkovich] reference describes a cloned DNA sequence encoding a retinoic acid receptor protein which is 90% homologous to the claimed sequence." Paper No. 15 at 3. As may be the case with chemical compounds, 90% of the elements in a claimed compound may be the same as the elements in a prior art compound. Obviousness, however, is measured by the differences between the claimed compound and the prior art compound, and whether these differences would have been obvious to a person of ordinary skill in the art. Graham v. John Deere Co., 383 U.S. 1, 148 U.S.P.Q. 459 (1966). No attempt has been made to explain why the 85% difference at one end of the gene and the 78% difference at the other end of the gene would have been obvious to a person of ordinary skill in the art.

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The question posed by the C.C.P.A. in In re Stemniski, 444 F.2d 581, 170 U.S.P.Q. 343, is relevant here:

> . . . [W]hat on this record - - - other than abstract, theoretical or academic considerations - - - would lead one of ordinary skill to change the structure of the reference compounds to obtain the claimed compounds?

444 F.2d at 586, 170 U.S.P.Q. 347. Appellants submit that there cannot be obviousness of structure, or particularly of the subject matter as a whole, when no apparent purpose or result is to be achieved, no reason or motivation to be satisfied, by modifying Petkovich's compound to change its nucleotide sequence to encode a different protein. The Examiner has not shown otherwise.

The issue of patentability of a claimed compound over a reference showing an assertedly related compound, is not without difficulty. In re Thompson, 119 U.S.P.Q. 254, 255 (Bd. App. 1954). Where, however, a comparison of the structure of the claimed compound with the structure of the prior art compound shows that the structures are related, it is incumbent on the Examiner to cite authority leading to the conclusion that the relationship was one recognized by workers in the field as leading to equivalent or similar products. Id. Such a showing has not been made in the present case. No showing has been made that a person of ordinary skill in the art would recognize that the structural relationship between Appellants' DNA encoding RAR-β and Petkovich's DNA encoding RAR-α would lead to equivalent or similar products. Surely it cannot be contended that the Hauptmann et al. and Krust et al. references suggest their equivalency.

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The patentability of a chemical compound does not depend on the similarity of its formula to that of another compound but of the similarly of the former compound to the latter. In re Papesch, 315 F.2d 381, 391, 137 U.S.P.Q. 43, 51 (CCPA 1963). Despite structural similarities the Examiner may perceive, Appellants' RAR-β and Petkovich's RAR-α are different receptors. The differences in structure alone are sufficient to render Appellants' cloned DNA sequence both unexpected and unobvious over the gene encoding the retinoic acid receptor of Petkovich et al., even when combined with the teachings of Hauptmann et al. and Krust et al.

The Examiner asserts that the disclosure of the cited references would have provided the skilled artisan with the techniques needed to isolate Appellants' cloned DNA sequence encoding RAR-β. See Paper No. 23 at 2. Appellants are claiming compounds and compositions, not methods of making them. Thus, the Examiner's focus on the prior art methods is misplaced. See In re Bell, 26 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1993) ("Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made.")

It is undisputed that the RAR-β gene was unknown prior to Appellants' discovery. The Examiner, in Paper No. 21 at page 3, relied on the Discussion section of the Petkovich et al. reference where Petkovich et al. speculate on the isolation of members of the retinoic acid receptor family using their disclosed teachings:

> The approach used here to clone hRAR [RAR-α] could obviously be used to isolate further members of the

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> nuclear receptor multigene family which may be expressed in embryonic or adult tissues. Chimaeric receptors similar to RAR-ER.CAS should be useful to identify "unknown" natural ligands or putative ligands unavailable in labelled forms.

Petkovich et al. at 450; emphasis added. What Petkovich et al. suggested was that their techniques "could" be used to isolate unknown members of the retinoic acid receptor family. The fact that one "could" isolate unknown retinoic acid receptors is not the test of obviousness. See In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) ("The mere fact that the prior could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.")

Neither Hauptmann et al. nor Krust et al. suggest any modifications to the structure of the DNA of Petkovich et al. Hauptmann et al. relates to a novel class of human type I interferon (INF). New sequences related to IFN-α are isolated using a human INF-α2 DNA probe. The reference is silent with regard to the isolation of other classes of molecules, much less, members of the retinoic acid receptor family. Thus, the combined teachings of Petkovich et al. and Hauptmann et al. would not have suggested to the skilled artisan the modifications to Petkovich's DNA to obtain Appellants' cloned DNA sequence.

Krust et al. similarly fail to overcome the deficiencies of Petkovich et al. Krust et al. cloned and sequenced the chicken oestrogen receptor. When the amino acid sequence of the chicken oestrogen receptor is compared with the sequence of the human oestrogen receptor, the human glucocorticoid receptor and v-*erbA*, Krust et al. showed that homologous regions could be identified.

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The reference is silent, however, as to the nature of the modifications that would have to be made to Petkovich's DNA to obtain any other member of the retinoic acid receptor family.

The disclosures of Petkovich et al., Hauptmann et al., and Krust et al. would not have suggested Appellants' gene encoding a receptor having the structure of the RAR-β receptor. The gene was unknown and the receptor it encodes was unknown. A *prima facie* case of obviousness has not been established, and claims 1-3, 10-14, 24-34, 40, 43-45 and 53 are patentable over the prior art.

B. CLAIMS 4-9 AND 57 ARE SEPARATELY PATENTABLE BECAUSE THE PRIOR ART DOES NOT TEACH APPELLANTS' DNA FRAGMENTS

Petkovich et al. cloned and sequenced the cDNA encoding RAR-α. Nowhere do Petkovich et al. direct the skilled artisan to select fragments of the cDNA, much less any of the six fragments recited in Appellants' claims 4-9 and 57.

Hauptmann et al. and Krust et al. similarly fail to disclose any fragments of the DNA sequence encoding the RAR-β receptor. Regardless of the patentability of Appellants' other claims, therefore, Appellants' claims 4-9 and 57 are separately patentable.

C. CLAIMS 39, 41, 42, 46-52, 54-56 AND 59 ARE SEPARATELY PATENTABLE BECAUSE THE PRIOR ART DOES NOT SHOW THE DNA SEQUENCE OF THESE CLAIMS

The disclosure of Petkovich et al. refers to the cDNA sequence that encodes the retinoic acid receptor RAR-α. The

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reference does not suggest or teach the 72 base pair nucleotide sequence of the DNA sequence, which extends from the sequence encoding RAR-β. As Hauptmann et al. and Krust et al. do not overcome this deficiency in the disclosure of Petkovich et al., Appellants' claims 39, 41, 42, 46-52, 54-56 and 59 are separately patentable over the cited prior art.

VII. CONCLUSION

The cloned DNA sequence of the present invention encodes a different and unique member of the retinoic acid receptor family. The nucleic acid sequence of the cloned DNA of RAR-β claimed by Appellants patentably distinguishes Appellants' invention from other members of the family. Because Appellants' DNA sequence is so vastly different in structure from the prior art, it is patentable over the prior art. Appellants respectfully request that the rejection be reversed.

If there are any other fees due in connection with the filing of this amendment, the Commissioner is authorized to charge any such fees to Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our deposit account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER

Dated: July 7, 1993

By: _____
Kenneth J. Meyers
Reg. No. 25,146

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APPENDIX

1. A cloned DNA sequence of *hap* gene, wherein the sequence has the formula:

ATGTTTGACTGTATGGATGTTCTGTCAGTGAGTCCTGGGCAAATCCTGGATTTCTACACTGCGAGT
CCGTCTTCCTGCATGCTCCAGGAGAAAGCTCTCAAAGCATGCTTCAGTGGATTGACCCAAACCGAA
TGGCAGCATCGGCACACTGCTCAATCAATTGAAACACAGAGCACCAGCTCTGAGGAACTCGTCCCA
AGCCCCCCATCTCCACTTCCTCCCCCTCGAGTGTACAAACCCTGCTTCGTCTGCCAGGACAAATCA
TCAGGGTACCACTATGGGGTCAGCGCCTGTGAGGGATGTAAGGGCTTTTTCCGCAGAAGTATTCAGA
AGAATATGATTTACACTTGTCACCGAGATAAGAACTGTGTTATTAATAAAGTCACCAGGAATCGAT
GCCAATACTGTCGACTCCAGAAGTGCTTTGAAGTGGGAATGTCCAAAGAATCTGTCAGGAATGACA
GGAACAAGAAAAAGAAGGAGACTTCGAAGCAAGAATGCACAGAGAGCTATGAAATGACAGCTGAGT
GTAAATACACCACGAATTCCAGTGCTGACCATCGAGTCCGACTGGACCTGGGCCTCTGGGACAAAT
TCAGTGAACTGGCCACCAAGTGCATTATTAAGATCGTGGAGTTTGCTAAACGTCTGCCTGGTTTCA
CTGGCTTGACCATCGCAGACCAAATTACCCTGCTGAAGGCCGCCTGCCTGGACATCCTGATTCTTA
GAATTTGCACCAGGTATACCCCAGAACAAGACACCATGACTTTCTCAGACGGCCTTACCCTAAATC
GAACTCAGATGCACAATGCTGGATTTGGTCCTCTGACTGACCTTGTGTTCACCTTTGCCAACCAGC
TCCTGCCTTTGGAAATGGATGACACAGAAACAGGCCTTCTCAGTGCCATCTGCTTAATCTGTGGAG
ACCGCCAGGACCTTGAGGAACCGACAAAAGTAGATAAGCTACAAGAACCATTGCTGGAAGCACTAA
AAATTTATATCAGAAAAAGACGACCCAGCAAGCCTCACATGTTTCCAAAGATCTTAATGAAAATCA
CAGATCTCCGTAGCATCAGTGCTAAAGGTGCAGAGCGTGTAATTACCTTGAAAATGGAAATTCCTG
GATCAATGCCACCTCTCATTCAAGAAATGATGGAGAATTCTGAAGGACATGAACCCTTGACCCCAA
GTTCAAGTGGGAACACAGCAGAGCACAGTCCTAGCATCTCACCCAGCTCAGTGGAAAACAGTGGGG
TCAGTCAGTCACCACTCGTGCAATAA,

wherein said DNA is in an isolated and purified form and encodes a retinoic acid receptor comprising a DNA binding domain and a hormone binding domain.

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2. DNA sequence as claimed in claim 1, which is free of human serum proteins, viral proteins, and nucleotide sequences encoding said proteins.

3. DNA sequence as claimed in claim 1, which is free of human tissue.

10. A DNA probe consisting essentially of a radionuclide bonded to the DNA sequence of claim 1.

11. A hybrid duplex molecule consisting essentially of the DNA sequence of claim 1 hydrogen bonded to a nucleotide sequence of complementary base sequence.

12. Hybrid duplex molecule as claimed in claim 11, wherein said nucleotide sequence is a DNA sequence.

13. Hybrid duplex molecule as claimed in claim 11, wherein said nucleotide sequence is a RNA sequence.

14. Hybrid duplex molecule as claimed in claim 11, wherein a radionuclide label is bonded to said DNA sequence.

24. A process for selecting a nucleotide sequence coding for *hap* protein or a portion thereof encoding a polypeptide capable of binding retinoic acid and functioning as a receptor from a group of nucleotide sequences comprising the step of determining which of said nucleotide sequences hybridizes to a DNA sequence as claimed in claim 1.

25. Process as claimed in claim 24, wherein said nucleotide sequence is a DNA sequence.

26. Process as claimed in claim 25, wherein said nucleotide sequence is selected by Southern blot technique.

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27. Process as claimed in claim 24, wherein said nucleotide sequence is a RNA sequence.

28. Process as claimed in claim 27, wherein said nucleotide sequence is selected by Northern blot technique.

29. Process as claimed in claim 24, wherein said process comprises the step of detecting a label bonded to said DNA sequence.

30. Process as claimed in claim 29, wherein said label is a radionuclide.

31. A recombinant vector comprising lambda-NM1149 having an EcoRI restriction endonuclease site into which has been inserted the DNA sequence as claimed in claim 1.

32. Plasmid pCOD20.

33. An E. coli bacterial culture in a purified form, wherein the culture comprises E. coli cells containing a plasmid, wherein a portion of said plasmid comprises the DNA sequence as claimed in claim 1.

34. Bacterial culture as claimed in claim 27, wherein said cells are comprised of E. coli strain TG-1.

40. A DNA sequence as claimed in claim 1, which is free of human tissue.

43. Hybrid duplex molecule as claimed in claim 11, wherein said nucleotide sequence is a DNA sequence.

44. Hybrid duplex molecule as claimed in claim 11, wherein said nucleotide sequence is a RNA sequence.

45. Hybrid duplex molecule as claimed in claim 11, wherein a radionuclide label is bonded to said DNA sequence.

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53. A recombinant DNA molecule comprising a DNA sequence of coding for a retinoic acid receptor, said DNA sequence coding on expression in a unicellular host for a polypeptide displaying the retinoic acid and DNA binding properties of RAR-β and being operatively linked to an expression control sequence in said DNA molecule.

54. Plasmid pPROHAP.

57. A DNA fragment comprising a portion of a DNA sequence, wherein the DNA sequence encodes a polypeptide of *hap* gene, and the DNA fragment comprises a nucleotide sequence selected from the group consisting of sequences:

(a) GTCAGGAATGACAGGAACAAGAAAAAGAAGGAGACTTCGAAGCAAGAATGC;

(b) GCTGAGTTGGAGATCTCACAGAGAAGATCCGA;

(c) GGGGTCAGTCAGTCACCACTCGTGCAA;

(d) AATGACAGGAACAAGAAAAAGAAGGAGACT;

(e) ATGTTTGACTGTATGGATGTTCTGTCAGTGAGTCCTGGGCAAATCCTGGATTT CTACACTGCG
AGTCCGTCTTCCTGCATGCTCCAGGAGAAAGCTCTCAAAGCATGCTTCAGTGGATTGACCCAAACCG GAA
TGGCAGCATCGGCACACTGCTCAATCA; and

(f) CATGAACCCTTGACCCCAAGTTCAAGTGGGAACACAGCAGAGCACAGTCCTAG CATCTCACCC
AGCTCAGTGGAAAACAGTGGGGTCAGTCAGTCACCACTCGTGCAA,

wherein sequence (a) encodes amino acid residues 151 to 167, sequence (b) encodes amino acid residues 175 to 185, sequence (c) encodes amino acid residues 440 to 448, sequence (d) encodes amino acid residues 153 to 162, sequence (e) encodes amino acid residues

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1 to 53, and sequence (f) encodes amino acid residues 413 to 448 of the mature retinoic acid receptor-β polypeptide.

4. A DNA fragment as claimed in claim 57, wherein the nucleotide sequence is sequence (a).

5. A DNA fragment as claimed in claim 57, wherein the nucleotide sequence is sequence (b).

6. A DNA fragment as claimed in claim 57, wherein the nucleotide sequence is sequence (c).

7. A DNA fragment as claimed in claim 57, wherein the nucleotide sequence is sequence (d).

8. A DNA fragment as claimed in claim 57, wherein the nucleotide sequence is sequence (e).

9. A DNA fragment as claimed in claim 57, wherein the nucleotide sequence is sequence (f).

59. A DNA sequence comprising a nucleotide sequence:

CCCATGC
GAGCTGTTTGAGGACTGGGATGCCGAGAACGCGAGCGATCCGAGCAGGGTTTGTCTGGGCACCGT
ATGTTTGACTGTATGGATGTTCTGTCAGTGAGTGCTGGGCAAATCCTGGATTTCTACACTGCGAGT
CC
GTCTTCCTGCATGCTCCAGGAGAAAGCTCTCAAAGCATGCTTCAGTGGATTGACCCAAACCGAATG
GCAGCATCGGCACACTGCTCAATCAATTGAAACACAGAGCACCAGCTCTGAGGAACTCGTCCCAAG
CCCCCCATCTCCACTTCCTCCCCCTCGAGTGTACAAACCCTGCTTCGTCTGCCAGGACAAATCATC
AGGGTACCACTATGGGGTCAGCGCCTGTGAGGGATGTAAGGGCTTTTTCCGCAGAAGTATTCAGAAG
AATATGATTTACACTTGTCACCGAGATAAGAACTGTGTTATTAATAAAGTCACCAGGAATCGATCG
CAATACTGTCGACTCCAGAAGTGCTTTGAAGTGGGAATGTCCAAAGAATCTGTCAGGAATGACAGG
AACAAGAAAAAGAAGGAGACTTCGAAGCAAGAATGCACAGAGAGCTATGAAATGACAGCTGAGTTG
GACGATCTCACAGAGAAGATCCGAAAAGCTCACCAGGAAACTTTCCCTTCACTCTGCCAGCTGGGT
AAATACACCACGAATTCCAGTGCTGACCATCGAGTCCGACTGGACCTGGGCCTCTGGGACAAATTC

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AGTGAACTGGCCACCAAGTGCATTATTAAGATCGTGGAGTTTGCTAAACGTCTGCCTGGTTTCACT
GGCTTGACCATCGCAGACCAAATTACCCTGCTGAAGGCCGCCTGCCTGGACATCCTGATTCTTAGA
ATTTGCACCAGGTATACCCCAGAACAAGACACCATGACTTTCTCAGACGGCCTTACCCTAAATCGA
ACTCAGATGCACAATGCTGGATTTGGTCCTCTGACTGACCTTGTGTTCACCTTTGCCAACCAGCTC
CTGCCTTTGGAAATGGATGACACAGAAACAGGCCTTCTCAGTGCCATCTGCTTAATCTGTGGAGAC
CGCCAGGACCTTGAGGAACCGACAAAAGTAGATAAGCTACAAGAACCATTGCTGGAAGCACTAAAA
ATTTATATCAGAAAAAGACGACCCAGCAAGCCTCACATGTTTCCAAAGATCTTAATGAAAATCACA
GATCTCCGTAGCATCAGTGCTAAAGGTGCAGAGCGTGTAATTACCTTGAAAATGGAAATTCCTGGA
TCAATGCCACCTCTCATTCAAGAAATGATGGAGAATTCTGAAGGACATGAACCCTTGACCCCAAGT
TCAAGTGGGAACACAGCAGAGCACAGTCCTAGCATCTCACCCAGCTCAGTGGAAAACAGTGGGGTC
AGTCAGTCACCACTCGTGCAATAA,

wherein the DNA sequence is an isolated, synthetic, or cloned sequence.

39. A DNA sequence as claimed in claim 59, which is free of human serum proteins, viral proteins, and nucleotide sequences encoding said proteins.

41. A DNA probe consisting essentially of the DNA sequence of claim 59.

42. A hybrid duplex molecule consisting essentially of the DNA sequence of claim 59 hydrogen bonded to a nucleotide sequence of complementary base sequence.

46. A process for selecting a nucleotide sequence coding for *hap* protein or a portion thereof encoding a polypeptide capable of

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binding retinoic acid and functioning as a receptor from a group of nucleotide sequences comprising the step of determining which of said nucleotide sequences hybridizes to a DNA sequence as claimed in claim 59.

47. Process as claimed in claim 46, wherein said nucleotide sequence is a DNA sequence.

48. Process as claimed in claim 47, wherein said nucleotide sequence is selected by Southern blot technique.

49. Process as claimed in claim 46, wherein said nucleotide sequence is a RNA sequence.

50. Process as claimed in claim 48, wherein said nucleotide sequence is selected by Northern blot technique.

51. Process as claimed in claim 46, wherein said process comprises the step of detecting a label bonded to said DNA sequence.

52. Process as claimed in claim 51, wherein said label is a radionuclide.

55. An E. coli bacterial culture in a purified form, wherein the culture comprises E. coli cells containing a plasmid, wherein a portion of said plasmid comprises the DNA sequence as claimed in claim 59.

56. Bacterial culture as claimed in claim 55, wherein said cells are comprised on E. coli strain DH5αF'.

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